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Research Article

Evaluation of the efficacy of tamsulosin with or without deflazacort for stone clearance after extracorporeal shockwave lithotripsy for upper ureteral and renal calculi

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ABSTRACT

Background: Medical expulsive therapy in the form of alpha blockers, corticosteroids, calcium channel blockers is being used with success for medical treatment of lower ureteric calculus. Adjunctive use of these therapeutic agents in post extracorporeal shockwave lithotripsy period is also being tried.With this background, we evaluated the efficacy of tamsulosin with or without deflazacort for various outcome factors after ESWL of upper ureteral and renal calculi.
Methods: A Prospecive study during period from February 2014 to April 2015 including a total of 90 patients with solitary upper ureteral or renal calculus who underwent ESWL was conducted. Patients were divided into three groups. Group A(30 patients) were given standard therapy (analgesics and antibiotics for 5 days), Group B (30 patients) were given standard plus tamsulosin (0.4 mg once daily) for 4 weeks and Group C (30 patients) were given standard therapy plus tamsulosin (0.4 mg once daily) and deflazacort (6 mg twice daily) for 4 weeks . Patients were evaluated at 2 and 4 weeks post ESWL with X ray KUB and USG.
Results: At the end of 4 weeks, 10, 17, and 26 patients in group A, B and C respectively cleared their stones. Out of these 2, 6 and 19 patients in group A, B and C respectively cleared their stones in first 2 weeks. Clearance in group C was significantly higher as compared to group A and B.
Conclusions: Addition of alpha-blocker tamsulosin along with deflazacort post ESWL for renal and upper ureteric calculi increases the stone expulsion rate and reduces the expulsion duration as shown by highly statistically significant results in group C.

Keywords: Tamsulosin, Deflazacort, Extracorporeal shockwave lihotripsy

INTRODUCTION

Genitourinary calculus disease is one of the common problems of modern era and with increasing incidence has become a challenge to society and medical fraternity. There are various modalities by which a calculus disease can be treated and the outcome of these depends on various factors. Extracorporeal shockwave lithotripsy (ESWL) is still one of the commonest methods used, though the drawbacks compared to invasive procedures are lesser clearance rate at shorter term and more overall time to clearance. Various modifications have been tried to overcome these drawbacks. In this study we evaluated the efficacy of tamsulosin with or without deflazacort for stone clearance after extracorporeal shockwave lithotripsy for upper ureteral and renal calculi.

METHODS

This was a prospective study during period from February 2014 to April 2015. This study included a total of 90 patients with either solitary upper ureteral or renal

calculus after excluding the patients as per the criteria mentioned in the Table 1. Out of these, 50 patients were male and 40 were female. The age ranged from 18 years to 58 years. Total number of patients with solitary renal stone was 63 and ureteric were 27. Based on the post ESWL treatment received, patients were allocated into three groups. Each group had 21 renal and nine ureteric calculus. All the patients included in the study had pre-procedure ultrasonographic evaluation of abdomen and digital intravenous urography performed. Only those patients whose stones were visualized in both ultrasonography and intravenous urography were included. For solitary renal calculus, patient with calculus in upper or mid calyx lesser then two centimetre (cm) after excluding the criteria from Table 1 was included. For solitary ureteral calculus, patient with calculus in upper ureter lesser then one cm after excluding the criteria from Table 1 were included. Upper ureter was defined as ureteric segment from pelvi-ureteric junction upto the upper border of sacroiliac junction. All patients meeting the inclusion criteria were subjected to ESWL by Dornier compact sigma machine and received 3000 shockwaves. Fluoroscopy was used for stone localization during lithotripsy. Patients whose stones did not fragment in 3000 shockwaves (confirmed by fluoroscopy) were excluded from study. Out of the three groups, group A was the control group and given standard therapy (oral cefuroxime 500 mg for three days twice daily), Group B received standard therapy plus tamsulosin (0.4 mg once daily for four weeks) and Group C received standard therapy plus tamsulosin (0.4 mg once daily for four weeks) and deflazacort (6 mg twice daily for four weeks). Digital radiograph (x-ray) of KUB region and abdominal ultrasound were taken at two and four weeks after the ESWL session in all the patients.

Table 1: Exclusion criteria.

S. No	Criteria
1.	Morbidly obese patients
2.	Uncorrected coagulopathy
3.	Active urinary tract infection.
4.	Pregnant and pediatric patients.
5.	Solitary functioning kidney.
6.	Chronic kidney disease.
7.	Previously operated for stone disease.
8.	Any renal stone more than 2 cm or any stone in lower pole of kidney.
9.	Upper ureteral calculus more than 1 cm
10.	Bilateral renal or bilateral ureteral calculi

For defining the success patients were considered stone free when there was a complete clearance of all stone fragments or the presence of clinically insignificant fragments, which were defined as asymptomatic fragments less than four mm. Failure was considered when stone fragment equal to or more than four mm was present at the end of four weeks.

Permission for conducting this study was taken from the institutional ethical clearance committee.

RESULTS

All the patients were evaluated with ultrasonography of abdomen and digital radiograph (X ray) of KUB region after 2 weeks and 4 weeks of ESWL.

At the end of 4 weeks, 10 patients in group A, 17 patients in group B, and 26 patients in group C cleared their stones respectively. Out of these, 2 patients in group A, 6 patients in group B and 19 patients in group C respectively cleared their stones in first 2 weeks. Results after 2 weeks are summarized in Table 2 and Figure 1 and results after 2 weeks are summarized in Table 3 and Figure 2.

Table 2: Results after 2 weeks.

Group	Stone cleared	Stone not cleared
A	2 (6.7)	28 (93.3)
B	6 (20.0)	24 (80.0)
C	19 (63.3)	11 (36.7)

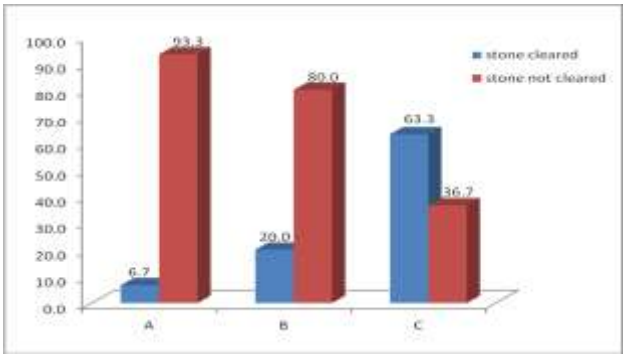

Figure 1: Calculus clearance after two weeks.

Table 3: Results after 4 weeks.

Group	Stone cleared	Stone not cleared
A	10 (33.3)	20 (66.7)
B	17 (56.7)	13 (43.3)
C	26 (86.7)	4 (13.3)

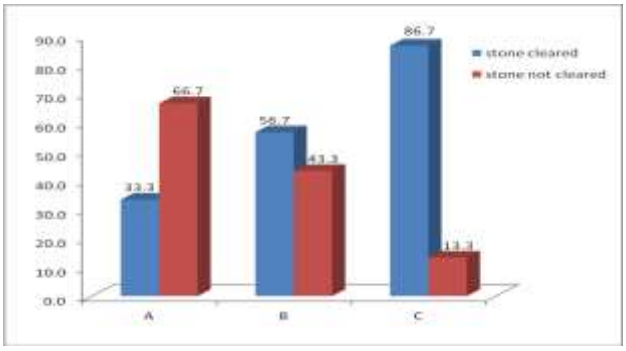

Figure 2: Calculus clearance after four weeks.

The results of this study, analysed using non parametric Kruskal-Wallis Test as the outcome of stone expulsion (at the end of second and fourth week) were measured as stone cleared or stone not cleared. Results of Kruskal-Wallis Test indicate that at second week the mean ranks of the scores (Score 1 for success and score 0 for failure) were 35.00 for Group A, 41.00 for Group B and 60.5 for Group C. The Group C was observed with the highest mean ranks and this was highly significant with the other two groups (χ^2=24.801; p<0.0001). Similarly at fourth week the mean ranks of the scores were 34.00 for Group A, 44.50 for Group B and 58.0 for Group C and at the end of this follow up Group C was showed the highest mean ranks with a highly significant difference with other two groups (χ^2=17.519; p<0.0001) (Table 4a and 4b).

Table 4a: Kruskal -Wallis test.

	Group	N	Mean Rank
Second week	A	30	35.00
	B	30	41.00
	C	30	60.50
	Total	90	
Fourth week	A	30	34.00
	B	30	44.50
	C	30	58.00
	Total	90	

Table 4b: Kruskal Wallis test statistics.

	Week 2	Week 4
Chi-Square	24.801	17.519
df	2	2
Asymp. Sig.	0.000	0.000

At the end of second week, individual comparisons of the outcome showed that though group A and group B were not having significant difference (P > 0.05), the difference between group A versus group C ($\chi^2_{A/C}$ =21.17; P<0.0001) and between group B versus group C ($\chi^2_{B/C}$ =11.59; P<0.0001) were highly significant showing a higher success rate in group C compared with its other counterparts.

At the end of fourth week, individual comparisons of the outcome showed that though group A and group B were not having significant difference (P > 0.05), the differences between group A versus group C ($\chi^2_{A/C}$ =17.78; P<0.0001) and between group B versus group C ($\chi^2_{B/C}$ =6.65; P<0.001) were highly significant showing a higher success rate in group C compared with its other counterparts.

DISCUSSION

Renal calculus disease is one of the most common afflictions of modern society and has been described since antiquity. With Westernization of global culture, however, the site of stone formation has migrated from the lower to the upper urinary tract. The lifetime prevalence of kidney stone disease is estimated at 1% to 15%, with the probability of having a stone varying according to age, gender, race, and geographic location.

Revolutionary advances in the minimally invasive and noninvasive management of stone disease over the past two decades have greatly facilitated the ease with which stones are removed. Out of the various treatment modalities available for upper ureteral and renal calculi, Extracorporeal Shockwave Lithotripsy (ESWL) still remains the preferred treatment for small and medium sized calculi among treating surgeons and more so among the patients, especially because of its non invasiveness. In February 1980 ESWL was first used for treatment in human and was approved by the U.S. Food and Drug Administration in 1984.

As a general consensus for patients harboring nonstaghorn stones smaller than 10 mm, ESWL is usually the primary approach. For patients with stones between 10 and 20 mm, ESWL can still be considered a first-line treatment unless factors of stone composition, location, or renal anatomy suggest that a more optimal outcome may be achieved with a more invasive treatment modality (Percutaneous Nephrolithotomy or Ureteroscopy). Patients with stones larger than 20 mm should primarily be treated by Percutaneous Nephrolithotomy (PNL) unless specific indications for ureteroscopy are present.

The human ureter contains α-adrenergic receptors along its entire length, with the highest concentration in its distal part. Stimulation of these α-receptors increases the force of ureteral contraction and the frequency of ureteral peristalsis, whereas antagonism of these receptors produces the opposite effects.[1,2] Malin and colleagues first demonstrated the presence of α-adrenergic receptors in the human ureter in 1970.[1]

Alpha-1-adrenergic receptor antagonists have some degree of selectivity for the detrusor and the distal ureter and have therefore been investigated for their potentiality to promote stone expulsion and decrease pain. The likely mechanism that α-blockers facilitates stone passage has been to reduce ureteral spasm, increase pressure proximal to the stone, and relax the ureter distal to the stone.[3] The rationale in using α_1 antagonists in medical expulsive therapy (MET) has been attributed to its capability of decreasing the force of ureteral contraction, decreasing the frequency of peristaltic contractions, and increasing the fluid bolus volume transported down the ureter.[4-6]

The major drawbacks of ESWL as compared to other invasive procedures are poor stone clearance, more time to clearance and more post procedural colicky episodes because of fragment impaction. Many adjunctive methods have been applied to reduce these drawbacks and few have stood the test of the time. Recently there have been reports suggesting the use of alpha blockers

and low dose steroids for facilitating lower ureteral calculus expulsion. Once a calculus is lodged at a particular site for prolonged period, it induces mucosal edema all around it which leads to its impaction and hinders its passage along the urinary tract. Usage of low dose steroids like deflazacort helps in reducing this edema and hence impaction, thus facilitating the passage of calculus without any significant side effects (because of low dose). Though successful use of these adjunctive measures for medical expulsive therapy for lower ureteric calculus have been reported many a times, there are hardly any trials of using these for upper ureteric and renal calculus. Taking into consideration two things, first that any fragmented calculi will have to pass the lower ureteric segment and secondly that there is gross mucosal edema around impacted ureteric or renal calculi which further increases after ESWL, we have tried adjunctive use of tamsulosin and deflazacort after ESWL for better stone clearance. In this study we evaluated the efficacy of tamsulosin with or without deflazacort for various outcome factors after ESWL for upper ureteral and renal calculus.

Bhagat, et al performed a prospective, double-blind, randomized placebo controlled study over a period of 1 year involving 60 patients with a solitary renal or ureteral calculus undergoing shock wave lithotripsy.[7] The control group (30) received 0.4 mg tamsulosin and the study group (30) received placebo daily until stone clearance or for a maximum of 30 days. The overall clearance rate was 96.6% (28 of 29) in their study group and 79.3% (23 of 29) in the control group ($p = 0.04$). With larger stones 11 to 24 mm the difference in the clearance rate was significant ($p = 0.03$) but not so with the smaller stones 6 to 10 mm ($p = 0.35$). The average dose of analgesic used was lower with tamsulosin than with controls, without statistical significance. Steinstrasse resolved spontaneously in the tamsulosin group whereas 25% (2 of 8) required intervention in the placebo group. They concluded that the alpha-blocker tamsulosin seemed to facilitate stone clearance, particularly with larger stones during shock wave lithotripsy for renal and ureteral calculus. It also appeared to improve the outcome of steinstrasse. In comparison to Bhagat, et al, though clearance rates in tamsulosin group increased in our group as well, but they were found to be insignificant. Only with the addition of deflazacort to tamsulosin, clearance rates improved to a significant level.

Gamal et al concluded that administration of α_1-blocker (doxazosin) after SWL improves clinical success in patients for renal and upper ureteral stones, decreases the time of fragments expulsion, and decreases the occurrence of recurrent renal colic.[8] Park, et al concluded that in a single proximal ureteral stone tamsulosin helps in the earlier clearance of stone fragments and reduces the expulsion period of stone fragments after ESWL.[9] Hussein, et al in a prospective randomized controlled study concluded that tamsulosin significantly increases stone clearance after SWL of renal stones.[10] It decreases the pain and amount of analgesics needed, with a low rate of side-effects. Similarly Zhu Y, et al in a meta analysis concluded that treatment with tamsulosin after ESWL appears to be effective in assisting stone clearance in patients with renal and ureteral calculi.[11] All these above mentioned studies have used tamsulosin alone as an adjunctive procedure to ESWL and have found it to be effecticve. In our experience addition of deflazacort, a low dose steroid, will significantly improve the ESWL outcomes.

Dellabella M performed a randomized study to assess the clinical efficacy of the addition of a corticosteroid drug to tamsulosin in the medical-expulsive therapy of distal ureterolithiasis and concluded that the use of a corticosteroid drug in association with tamsulosin seemed to induce more rapid stone expulsion.[12] Porpiglia F. performed a prospective study from October 1998 to September 2000 which involved 80 patients. All the patients underwent ESWL with Sonolith 4000+.[13] The patients were randomly divided into two groups: 40 patients (group one) received an "adjunctive" treatment with oral medical therapy (nifedipine and deflazacort); the other 40 patients (group two) were used as the control group. Complete fragment expulsion occurred in 30 (75%) of the 40 patients of group one and in 20 (50%) of the 40 patients of group two at the endpoint. A statistically significant difference was observed in the stone-free rate ($P = 0.02$). There results have shown the role that adjunctive medical therapy with nifedipine and deflazocort given after an ESWL procedure can play in increasing the success rate of ureteral stone treatment. Though both the above mentioned studies have used steroids to augment calculus expulsion, they have confined their study group to ureteral calculus only. If steroids are useful in reducing peri-calculus edema in ureter as seen by results of all the above studies, they should be beneficial for renal calculus as well as proved by our results.

Haider Raheem Mohammad et al conducted a randomized single-blind clinical trial on 30 patients with renal pelvis or calyceal calculi sized between 10 mm and 20 mm.[14] Post ESWL Patients were subdivided into two groups, 15 patients received starch as placebo supplied in capsules for 12 weeks, and 15 patients received tamsulosin capsule 0.4 mg/d for 12 weeks. All patients underwent follow-up examinations at 4, 8, and 12 weeks after extracorporeal shock wave lithotripsy, by kidney, ureter, and bladder radiography and ultrasonography Tamsulosin had an insignificant effect on the stone-free rate ($P = 0.788$ at 4 weeks),($P = 0.175$ at 8 weeks) and ($P = 0.299$ at 12 weeks). Overall, they concluded that tamsulosin had no significant effect on the stone-free rate. Treatment with tamsulosin after extracorporeal shock wave lithotripsy to assist calculus clearance is neither effective, nor implying a shorter expulsion time. The results of this study are contradictory to the results of our as well as most other studies. This may be because authors have in general included renal calculus between 10 mm to 20 mm. It is a

well established fact that lower calyceal calculus more then 10 mm has poorer outcomes in ESWL until all other anatomical factors are considered. Another limitation affecting the results of this study may be lesser number of patients included.

For defining the success and determination of stone free rate after shock wave lithotripsy we followed patients with plain X ray KUB in addition to abdominal ultrasound. Cheung et al. in their study as well reported that the usage of plain abdominal radiography plus ultrasound are highly sensitive for screening renal & ureteral obstruction after primary in-situ SWL for renal & ureteral calculi and it can save up to 74% of patients from potential risk of radiation hazards of IVU.[15]

Andreas Skolarikos et al, conducted a meta-analysis to evaluate the efficacy of Medical Expulsive Therapy (MET) in improving stone-free rate and stone expulsion time, after extracorporeal Shock Wave Lithotripsy (SWL) for upper urinary stones.[16] Their results demonstrated the efficacy of α-blockers, nifedipine, Rowatinex and Uriston in increasing stone clearance. In addition, the time to stone elimination, the intensity of pain, the formation of steinstrasse, and the need for auxiliary procedures were reduced mainly with alpha-blockers. Expulsion rate was not correlated with the type of alpha-blocker, the diameter, and the location of stone. Our results show that medical expulsive therapy for residual fragments after shock wave lithotripsy should be implemented in clinical practice.

Though the results of our study were comparative to the previous similar studies, it was not devoid of limitations being a single institution based study. Another limitation of our study was that we could not assess the efficacy of adjuvant therapy to reduce post ESWL colicky episodes.

CONCLUSIONS

In conclusion the alpha blocker (Tamsulosin) along with Deflazacort administration after SWL for renal and ureteral stones has a marked effect on stone clearance rate. When ESWL for a renal or upper ureteric calculus is indicated, adjunctive use of tamsulosin along with deflazacort should be considered in post ESWL period. Tamsulosin alone in post ESWL period increases the overall clearance rates, but when deflazacort is added along with tamsulosin, duration of fragment clearance is further shortened. 4 weeks duration of therapy seems to be justified.

Although no current specific guidelines exsist, the results of adjunctive medical expulsive therapy in the form of tamsulosin and deflazacort post ESWL are encouraging. Further studies are likely to provide additional data which can help in formulating standardized guidelines.

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